Cefoxitin Disposition During Peritoneal Dialysis

WAYNE L. GREAVES,1 JOHN H. KREEFT,1 RICHARD I. OGILVIE,1* AND GEOFFREY K. RICHARDS2

Clinical Pharmacology Division, Department of Medicine,1 and Department of Microbiology,2 Montreal General Hospital, Montreal, Quebec H3G 1A4, and Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

The pharmacokinetic disposition of 2 g of cefoxitin administered intravenously over 30 min was determined in six patients undergoing continuous ambulatory peritoneal dialysis for chronic renal failure. During the 6-h dialysate dwell time after the drug infusion, the mean apparent volume of distribution for cefoxitin was 0.267 liter/kg (range, 0.201 to 0.325 liter/kg), and the mean elimination t1/2 from plasma was 7.8 h (range, 5.5 to 13.1 h). The peritoneal clearance, averaging 1.51 ml/min (range, 0.58 to 2.35 ml/min), was only 7.4% of the mean plasma clearance of cefoxitin. Cefoxitin clearance was reduced in patients with renal failure and was not increased by peritoneal dialysis.

Continuous ambulatory peritoneal dialysis is a self-dialysis technique used as an alternative mode of therapy in patients with end-stage renal disease. The major drawback to its use is frequent peritonitis caused by a variety of gram-positive and gram-negative bacteria (6–8). Cefoxitin, a cephamycin with broad-spectrum bactericidal activity and with a high tolerance in patients with impaired renal function (9), is of potential use in patients who develop bacterial peritonitis. Therefore, the rate of clearance of the drug from the body during continuous ambulatory peritoneal dialysis is of importance in the designing of adequate dose schedules for these patients.

MATERIALS AND METHODS

Six patients (three males and three females) undergoing continuous ambulatory peritoneal dialysis with previously determined creatinine clearances of <10 ml/min volunteered for the study (see Table 1). Each subject signed the standard Montreal General Hospital consent form for participation in a clinical study. With few minor modifications, continuous ambulatory peritoneal dialysis was performed as described by others (5, 7). Commercial dialysate solution (Baxter Laboratories) containing 1.5% dextrose was used, and each patient was studied during the 6-h dialysate dwell time of the first exchange (beginning at 0800 h) on the day of study. All patients had a physical exam, a base-line 12-channel Sequential Multiple Analyzer study, a complete blood count, erythrocyte sedimentation rate assay, and urinalysis (when possible) before being studied. Patients with hepatic disease, anemia (hemoglobin, <6 g), or a known drug allergy were excluded.

Cefoxitin (2 g) was infused intravenously over 30 min at the onset of the dialysis period in the early morning. Blood samples (5 ml) were drawn through an indwelling venous cannula kept filled with heparinized saline (1,000 U/liter). These were taken at 0, 30, 45, 60, 90, and 120 min and at 3, 4, 5, and 6 h after infusion. Urine specimens were obtained from those three patients who were not anuric and produced urine during the study period. Blood samples and samples of urine and dialysate fluid were assayed for antimicrobial activity of cefoxitin.

The approximate concentrations of cefoxitin in the samples were first determined by a standard serial dilution tube technique. With 0.5-ml volumes of tryptone soya broth (Oxoid Ltd; CM 129), doubling dilutions of serum (or urine or peritoneal dialysate) were made in duplicate for the range of 1:2 to 1:512. Each tube was inoculated with a log-phase culture of Escherichia coli NCTC 10418 to achieve a density of 106 colony-forming units per ml. After overnight aerobic incubation at 37°C, the tubes were read turbidimetrically. The endpoints were defined as the tubes containing the lowest concentration of serum exhibiting inhibition of bacterial growth. A standard of 5 mg of cefoxitin per liter in horse serum was diluted in parallel from 1:2 to 1:512 for each batch of assays. When the assay was performed on urine or dialysate samples, appropriate cefoxitin control solutions were used.

With these preliminary data as guides, the sera were reassayed by a variable-volume tube technique. Each serum sample was bulk diluted to give a test concentration of approximately 15 mg of cefoxitin per liter. For each test, 10 dilutions were made in duplicate. Each tube contained 1.5 ml of tryptone soya broth, inoculated with a log-phase culture of E. coli NCTC 10418 to a concentration of 105 colony-forming units per ml. To the first tube was added 0.02 ml of test serum. To the second tube was added 0.04 ml, and this was continued with increments of 0.02 ml of serum per tube until the final tube, which received 0.2 ml. For each batch of assays, a control serum containing 15 mg of cefoxitin per liter was set up in parallel, using the same increments of 0.02 ml per tube. After overnight incubation at 37°C, the tubes were read turbidimetrically. The endpoint was defined as the tube containing the least serum but showing no growth. The control assay result was constant at a cefoxitin concentration...
of 0.75 mg/liter. The assay was accepted if the end-point of the test samples fell within the dilution range above 0.75 mg/liter (tubes 4 through 10). The cefoxitin concentration was calculated from the dilution at the endpoint of the test samples as compared with that in the control standard. There was no variance seen in the duplicate analyses. To test the stability of cefoxitin in the peritoneal dialysis fluid, concentrations of 5 and 100 mg/liter in the commercial dialysate were reasayed after 24 h of incubation. There were no changes in measured drug concentrations, indicating stability.

Kinetic analysis was begun by determining the elimination constant by using least-squares linear regression on the log plasma cefoxitin concentration versus time curve from 1.5 to 6.0 h. The apparent volume of distribution \( V_d \) (area) was calculated with the formula: \( V_d \) (area) = dose/(\( K_a \times \text{AUC}^{(c)} \)), where \( K_a \) is the elimination constant and \( \text{AUC}^{(c)} \) is the area under the curve. The area under the curve of plasma concentration over time from 0 to 6 h was calculated by the trapezoidal method. The area from the last concentration to \( \infty \) was calculated from the quotient of the last concentration and the slope obtained in the regression analysis mentioned above. The quotient of the amount of cefoxitin eliminated and the area under the curve for the given time period was used to calculate clearance values.

**RESULTS**

(i) Kinetic disposition. The infusion of 2 g of cefoxitin over 30 min resulted in a mean peak plasma concentration of 161 mg/liter (range, 121 to 197 mg/liter) (Table 1). The mean elimination \( t_{1/2} \) from plasma was 7.8 h (range, 5.5 to 13.1 h), and the mean volume of distribution was 15.6 liters (range, 11.6 to 22.7 liters) or 0.272 liters/kg (range, 0.215 to 0.349 liter/kg) (Table 2). The volume of distribution (extrapolated) calculated from the quotient of the dose and the extrapolated concentration at zero time was only marginally larger (0.267 liter/kg; range, 0.201 to 0.362 liter/kg) than the volume of distribution (area).

The peritoneal clearance of cefoxitin over the 6-h period after drug infusion averaged 1.44 ml/min (range, 0.58 to 2.35 ml/min), representing a very small portion (7.4%) of the mean plasma clearance of 20.43 ml/min (range, 16.95 to 26.82 ml/min) over the same time period. In two of the three patients who produced urine, the renal clearance was 4.1 and 4.8 times larger than was the peritoneal clearance of cefoxitin.

(ii) Adverse effects. One patient complained of mild irritation lasting 1 day at the site of drug infusion. This patient had a history of gallbladder disease and developed acute biliary colic 4 h after the study began. She was in considerable distress from pain which required the administration of meperidine but was asymptomatic 8 h later. Another patient also with a history of gallbladder disease developed jaundice and elevated tests of liver function approximately 24 h after the study began. A diagnosis of acute cholecystitis was made, and the patient recovered without sequelae after conservative management.

**DISCUSSION**

The plasma \( t_{1/2} \) of cephalosporins progressively increases as the rate of creatinine elimination decreases (1), and cefoxitin is no exception. Fillastre et al. (2) reported a plasma \( t_{1/2} \) of 0.8 h in normal subjects, as compared with a plasma \( t_{1/2} \) of 21.6 h in patients with very poor renal function. Garcia et al. (3) have observed a mean plasma \( t_{1/2} \) of 12 h (range, 7 to 20 h) in seven subjects with terminal renal failure, in contrast to a mean plasma \( t_{1/2} \) of 0.7 h in subjects with normal renal function. Patients with intermediate renal function (creatinine clearance between 12 and 62 ml/min) had plasma cefoxitin \( t_{1/2} \) values ranging from 1.5 to 12 h. In 10 patients with chronic renal failure (creatinine clearance, <5 ml/min), the plasma cefoxitin \( t_{1/2} \) averaged 10 h between dialysis sessions and 4 h during a 6-h hemodialysis session. Fillastre et al. (2) observed a plasma \( t_{1/2} \) of 13.2 in five patients with a creatinine clearance of <10 ml/min.

In this experiment, involving six patients with chronic renal failure (creatinine clearance, <10 ml/min), the plasma cefoxitin \( t_{1/2} \) averaged 7.8 h during a 6-h period of peritoneal dialysis. The relatively short sampling time necessitated by the duration of dialysis may have influenced the accuracy of our \( t_{1/2} \) determinations. Although we do not have plasma cefoxitin \( t_{1/2} \) values between dialysis sessions, as these patients were on continuous ambulatory peritoneal dialysis, clearance of cefoxitin by the peritoneal route was extremely low, averaging only 1.5 ml/min. Two

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Plasma concn (mg/liter) at following time (h):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>121</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>197</td>
</tr>
<tr>
<td>4</td>
<td>197</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
</tr>
</tbody>
</table>
of the patients who produced urine during the 6-h dialysis period had renal clearances of cefoxitin approximately four times higher than peritoneal clearances. It is of interest that peritoneal dialysis also minimally influences the \( t_{1/2} \) of cefazolin or cefamandole, whereas it reduces the \( t_{1/2} \) of cephalothin and cephaloridine (1). In contrast, hemodialysis decreases the \( t_{1/2} \) of cefoxitin, cefazolin, cephaloridine, cephalaxin, and cephalotriate but only minimally influences the \( t_{1/2} \) of cephalothin and cefamandole (1, 3).

Garcia et al. (3) observed a relationship between plasma protein binding of cefoxitin and its apparent volume of distribution. Binding averaged 73% in patients with normal renal function and 42% in patients with terminal renal failure. The apparent volume of distribution averaged 0.160 liter/kg in patients with normal renal function and 0.370 liter/kg in patients with terminal renal failure. In patients with creatinine clearances of between 12 and 62 ml/min, the apparent volume of distribution averaged 0.263 liter/kg. In this experiment, the apparent volume of distribution averaged 0.272 liter/kg. One patient with the longest cepoxitin \( t_{1/2} \) (13.1 h) had the highest serum creatinine concentration (13.4 mg/dl) and the largest peritoneal clearance (2.35 ml/min). Although we did not measure plasma protein binding of cefoxitin, these results are consistent with reduced binding.

We conclude that cefoxitin clearance is related to renal function, as evidenced by reduced clearance in the presence of reduced renal function. The removal of cefoxitin by the dialysate fluid was not efficient in this study. Although dose schedules for cefoxitin should be modified in patients with diminished creatinine clearance, it is unlikely that further modifications would be required for patients undergoing continuous ambulatory peritoneal dialysis. This is in contrast to the additional cefoxitin doses required after hemodialysis treatments (4).

ACKNOWLEDGMENT

This work was supported in part by a grant-in-aid from W. Dorian, Director of Scientific Affairs, Merck Sharp & Dohme Canada, Limited.

LITERATURE CITED